IE PATENT APPLICATION No. 930590

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Patents Office

930590

ABSTRACT

The present invention relates to the use of aliphatic carbocyclic compounds that have pendant hydroxy groups for incorporating water-insoluble molecules as hydrophilic components of drug delivery systems for human or animal treatment.

In particular this patent describes a pharmaceutical formulation wherein the hydrophilic component contains in part a 17-ketosteroids along with aliphatic carbocyclic compounds that have pendant hydroxy groups, such as cyclodextrin (CD), and the likes, as well as mixtures thereof. In particular the 17-ketosteroids is Dehydroepiandrosterone (DHEA) and the cyclodextrin is hydroxypropyl-beta-cyclodextrin. The cyclodextrin is used with the 17-ketosteroid to give it hydrophilic characteristics.

The present invention also relates to the use of certain 17-ketosteroids as hydrophobic components of drug delivery systems. As hydrophobic elements, the 17-ketosteroids have been discovered to have beneficial rapid drug delivery characteristics hitherto unknown.

PATENT APPLICATION

INVENTOR: PATRICK T. PRENDERGAST

TITLE: THERAPEUTIC COMPLEXES

BACKGROUND TO THE INVENTION

Any prescribed drug dose is the result of compromise. One the one hand, all drugs are potentially poisonous, suggesting that the least possible amount should be administered. On the other hand, drugs become diluted in the blood and large amounts are degraded, taken up by healthy tissues or excreted without ever reaching the site of disease. Such wastage increases the need for high doses. Physicians balance these opposing pressures by prescribing doses they think will be high enough to control the patient's problem but low enough to avoid causing unacceptable damage to healthy tissues.

To reduce the risk and inefficiency associated with such guesswork, many laboratories are now developing drug-delivery systems that alter the pathways by which drugs travel through the body. The goal is to deliver the needed dose of medicine to diseased tissues but to bypass healthy ones, thereby improving the drug's ratio of effectiveness to toxicity.

Herein are described complexes of 17-ketosteroid of aliphatic carbocyclic compounds as pharmaceutical formulations which have been beneficial characteristics as complexes compared to each group administered as pharmaceutically formulated alone.

These beneficial characteristics of the complexes generally arise from the reduced chemical reactivity of 17-ketosteroids in complex form with aliphatic carbocyclic compounds. In particular reduced sulphation is observed when Dehydroepiandrosterone (DHEA) is administered. These complexes thus allow greater precision in determining the role of any biologically active compound, incorporated in the complex, as reduced metabolism is observed.

SUMMARY OF THE INVENTION

The present invention relates to the use of aliphatic carbocyclic compounds that have pendant hydroxy groups for incorporating water-insoluble molecules as hydrophilic components of drug delivery systems for human or animal treatment.

In particular this patent describes a pharmaceutical formulation wherein the hydrophilic component contains in part a 17-ketosteroid along with or combined with an aliphatic carbocyclic compounds that have pendant hydroxy groups, such as cyclodextrin (CD), and the likes, as well as mixtures thereof. In particular the 17-ketrosteroid is Dehydroepiandrosterone(DHEA) and the cyclodextrin is hydroxypropyl-beta-cyclodextrin. The cyclodextrin is used with te 17-ketosteroid to give hydrophilic characteristics. Additional therapeutic efficiency is obtained where DHEA is required as the active agent resulting from the fact that when DHEA is complexed with beta-cyclodextrin the compound is not readily transformed to DHEA-sulphate within the body. The benefits of this is readily understood in the treatment of AIDS especially in the knowledge of our findings as reported herewith.

The preparation of suitable hydroxypropyl-beta cyclodextrins is described, inter alia, in International Journal of Pharmaceutics 29:73-82 (1986) and in Journal of Pharmaceutical Sciences 75 (6):571-572 (1986). Also known, and contemplated for the purposes of the present invention are the hydroxypropyl-beta-cyclodextrins that are polyesters of cyclodextrins and are obtained by condensation of an excess of hydroxypropylene oxide with beta-cyclodextrin as described in U.S. Pat. No. 3,459,731 to Gzamera et al. Historically, cyclodextrins (CDs) have been used entensively in the pharmaceutical industry in oral formulations, parenteral formulations and suppositories. In practical terms, CD complexes improve drug stability, enhance solubility, promote faster absorption, reduce local irritation and result in improved bio-availability.

This method of using cyclodextrins has definite advantages over the classical method of dissolving in organic solvents. Complexation is favoured in cold, concentrated CD solutions. Equilibrium is shifted in warm, dilute solutions and molecules of interest or guest molecules are released. Stability is conferred to the guest molecule by protecting it from degradation due to heat, sublimation, enzymatic sulphation, oxidation and/or light. Improved bio-availability of components that have been complexed also occurs because their

homogeneous distribution is increased. Many of the 17-ketosteroids function as hormones and include sex hormones or precursors thereof and hormones which control metabolism. Dehydroepiandrosterone (DHEA) is one such 17-ketosteroids which is a precursor of both androgens and estrogens and additionally has important metabolic effects. DHEA has been found to suppress some of the metabolic disorders and liver cirrhosis, and reduces pain in ischemic heart disease, especially in angina pectoris, by restricting tissue respiration. DHEA has been used in the treatment of menopause, emotional instability, depression and stress. DHEA and related compounds are capable of reducing the colony forming ability of human peripheral blood mononuclear (PBM) cells infected with Epstein-Barr virus (a herpes virus) at concentrations of 10-100 uM (Carcinogenesis, Vol. 2, pp 883-886, 1981).

DHEA also inhibits complement activation and is therefore of value in the prophylaxis of Hereditary Angioneurotic Oedema (Hidvegi et al., Complement 1; 201, 1984). DHEA also prevents autoantibody formation in the murine model of Systemic Lupis Erythematosus (SLE) and many of the features of full-blown AIDS are considered to be similar to those of SLE (Lucas et al., J. Clin. Invest., 75: 2091, 1985).

Recent studies in animals demonstrate that DHEA has beneficial effects in obesity and breast cancer. Schwartz Cancer Res. 39:1129 (1979); Schwartz Nutrition and Cancer, 3:46 (1981), DHEA also has been shown to have antihypercholesterolic effects in lowering lipid levels in rats. Ben-David et al., Proc. Soc. Exp. Biol. Med., 20 125:1136 (1967).

The importance of hypercholesterolemia, an elevated low-density lipoprotein (LDL) cholesterol level, as a major risk factor for the development of ischemic heart disease is widely accepted.

Barrett-Connors et al., New Engl. J. Med. 315:1519 (1986) showed that individuals with low circulating levels of DHEA-S die of heart disease at a higher rate than normal subjects. The oral administration of DHEA (1600 mg/day) reduces total serum cholesterol and LDL levels by about 7.1 and 7.5 percent, respectively, in normal subjects.

The use of DHEA and other 17-ketosteroids as medication for the prophylaxis and therapy of a retrovirus infection or for complications arising therefrom, e.g., Acquire Immune Deficiency Syndrome (AIDS) has been reported in SCRIP No. 1422, June 21, 1989, page 21 and in British Pat. Publication No. 2,204,237 by Colthurst, Ltd. Oral administrations of relatively large doses of 1 to 2 grams per day has been

tested in AIDS patients and shown to improve their immune systems and lower viral HIV load. In such tests, DHEA was administered orally alone or in combination with immunomodulators. Liposomes carrying DHEA as a hydrophilic CD complex target HIV infected macrophages and Kuffer cells more directly and thus reduce the dosage required, this formulation prevent sulphation to inactivate DHEAS form in the plasma and deliver the required dosage to the infected target tissues.

CLAIMS

1. A pharmaceutical formulation wherein a therapeutic agent is complexed with one or more aliphatic carbocyclic compounds that have pendant hydroxy groups.

2. A pharmaceutical formulation wherein a 17-ketosteroid is complexed with one or more aliphatic carbocyclic compounds that have pendant hydroxy groups.

3. A pharmaceutical formulation according to Claim 1 wherein the 17-ketosteroid is Dehydroepiandrosterone (DHEA) thus restricting the enzymatic transformation of DHEA to DHEA-Sulphate within the body.

4. A pharmaceutical formulation according to Claim 1 and 2 wherein the aliphatic carbocyclic compounds that have pendant hydroxy groups is hydroxypropyl-beta-cyclodextrin (HPBCD).

5. A pharmaceutical formulation according to Claim 1,2,3 and 4 wherein the formulation is administered for the treatment of a viral infection in human or animal.

6. A pharmaceutical formulation wherein the therapeutic growth is interleukin-2.

7. A pharmaceutical formulation wherein the therapeutic growth is tumor necrosis factor.

8. A pharmaceutical formulation wherein the therapeutic growth is insulin.

9. A pharmaceutical formulation wherein the therapeutic growth is alpha-fetoprotein or antibodies to parts thereof.

10. A pharmaceutical formulation according to Claims 1,2 and 5 wherein the aliphatic carbocyclic compounds that have pendant hydroxy groups is gamma - cyclodextrin.

11. A liposomal drug delivery system wherein the hydrophobic component of the liposome is composed, in whole or in part, of a 17-ketosteroid.

12. A drug delivery system according to claim 11 wherein the 17-ketosteroid is dehydroepiandrosterone (DHEA).

13. A liposomal drug delivery system wherein a 17-ketosteroid is used to target the liposome to specific body tissue.

14. A drug delivery system according to claim 13 wherein the 17-ketosteroid is dehydroepiandrosterone (DHEA).

15. A drug delivery system according to claim 11, 12, 13, 14 wherein the therapeutic agent is removed rapidly from circulation.

16. A liposomal durg delivery system wherein the hydrophilic component contains in part a 17-ketosteroids along with one or more aliphatic carbocyclic compounds that have pendant hydroxy groups.

17. A drug delivery system according to claim 16 wherein the aliphatic carbocyclic compounds that have pendant hydroxy groups is hydroxypropyl-beta-cyclodextrin (HPBCD).

18. A drug delivery system according to claim 16 wherein the 17-ketosteroid is dehydroepiandrosterone (DHEA).

19. A liposomal drug delivery system wherein the therapeutic agent is totally or partialy a 17-ketosteroids.

20. A drug delivery system according to claim 19 wherein the 17-ketosteroid is dehydroepiandrosterone (DHEA).

21. A drug delivery system according to claim 20 wherein the therapeutic agent is complexed with one or more aliphatic carbocyclic compounds that have pendant hydroxy groups thus restricting the transformation of DHEA to DHEA-sulphate within the body.

ABSTRACT

The present invention relates to the use of aliphatic carbocyclic compounds that have pendant hydroxy groups for incorporating water-insoluble molecules as hydrophilic components of drug delivery systems for human or animal treatment.

In particular this patent describes a pharmaceutical formulation wherein the hydrophilic component contains in part a 17-ketosteroids along with aliphatic carbocyclic compounds that have pendant hydroxy groups, such as cyclodextrin (CD), and the likes, as well as mixtures thereof. In particular the 17-ketosteroids is Dehydroepiandrosterone (DHEA) and the cyclodextrin is hydroxypropyl-beta-cyclodextrin. The cyclodextrin is used with the 17-ketosteroid to give it hydrophilic characteristics.

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